Venous thromboembolism in advanced cancer

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Disclosures

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2. Advisor Board: Bayer
3. Grant: HIDDEN was funded by NIHR (RfPB)
To cover

1. Haemostasis oversight
2. The clinical trials informing practice non representative populations
3. Anticoagulants at the end of life
4. Thromboprophylaxis in the SPCU
5. Tranexamic and thrombotic risk
COAGULATION: The Formation of a Blood Clot

Stage I:
Platelets attach to the endothelium (blood vessel wall)

Stage II:
Platelets start to release fibrin and begin to seal the endothelium

Stage III:
The fibrin network traps the RBC, and completely seal the endothelium

Platelet

Endothelium (Blood Vessel Wall)

Red Blood Cells (RBC)

Connective Tissue

Fibrin Polymers
Schematic of the phase dynamics of blood clot contraction.

Phase 1
Initiation of Contraction

Phase 2
Linear Contraction

Phase 3
Mechanical Stabilization

- Red Blood Cell
- Platelet
- Fibrin

TIME
Clot presentation

- DVT: 7-14 days
- PE: 21 days
Clot stabilization and resorption

1. Initial stabilization: 5-14 days
2. Stable clot: 6 weeks
3. Resorption 4-12 weeks
Exclusion criteria to VTE clinical trials

1. ECOG>2
2. Prognosis < 3 months
3. Weight < 40kg
4. Deranged biochemistry
Anticoagulants and Hospices
RHESO study

- 22 SPCUs, 1199 patients
- CRB 9.8% (95% CI 8.3-11.6)

Clinically relevant bleeding = Major Bleeding + Clinically Relevant Non Major Bleeding
### Characteristics of patients

#### Reason for admission to the palliative unit

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>1091 (91.0)</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>929 (77.5)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>52 (4.3)</td>
</tr>
<tr>
<td>Cardiac or respiratory disease</td>
<td>49 (4.1)</td>
</tr>
<tr>
<td>AIDS*</td>
<td>7 (0.6)</td>
</tr>
</tbody>
</table>

#### Treatments received within 4 weeks prior to admission

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer treatment</td>
<td>0/1199</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>257 (21.4)</td>
</tr>
<tr>
<td>Targeted cancer therapy</td>
<td>35 (2.9)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>91 (7.6)</td>
</tr>
<tr>
<td>Growth factors</td>
<td>0/1199</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>At prophylactic (low) dose**</td>
<td>0/1199</td>
</tr>
<tr>
<td>At therapeutic (high) dose††</td>
<td>0/1199</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>527 (44.0)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>167 (14.0)</td>
</tr>
<tr>
<td>Antidepressive agents</td>
<td>6/1193</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>620 (52.0)</td>
</tr>
<tr>
<td>Antidepressive agents</td>
<td>304 (25.4)</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td>208 (17.3)</td>
</tr>
</tbody>
</table>
### Table 4: Univariate and multivariate analyses of potential risk factors for clinically relevant bleeding at 3 months

<table>
<thead>
<tr>
<th>Patient factor</th>
<th>With bleeding (n = 116)</th>
<th>Without bleeding (n = 1075)</th>
<th>Multivariate analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Male sex</td>
<td>63 (54.3)</td>
<td>479 (44.6)</td>
<td>1.31 (0.91–1.90)</td>
</tr>
<tr>
<td>Cancer</td>
<td>114 (98.3)</td>
<td>970 (90.2)</td>
<td>5.65 (1.40–22.9)</td>
</tr>
<tr>
<td>Previous surgery†</td>
<td>2 (1.7)</td>
<td>67 (6.2)</td>
<td>0.21 (0.05–0.87)</td>
</tr>
<tr>
<td>Previous bleeding†</td>
<td>38 (32.8)</td>
<td>134 (12.5)</td>
<td>3.36 (2.28–4.97)</td>
</tr>
<tr>
<td>Anticoagulant prophylaxis†</td>
<td>69 (59.5)</td>
<td>561 (52.2)</td>
<td>1.48 (1.02–2.15)</td>
</tr>
<tr>
<td>Antiplatelet therapy‡</td>
<td>44 (37.9)</td>
<td>288 (26.9)</td>
<td>1.67 (1.15–2.44)</td>
</tr>
</tbody>
</table>

Only factors with a *P* value ≤ 0.15 in the univariate analysis are presented. Because data were available in less than 75% of the cohort, only risk factors were included in the multivariate analysis. *According to the Fine and Gray method. †Within 4 weeks prior to inclusion or during hospitalization in the palliative care unit.
Study to identify current practice in patients with cancer associated thrombosis at the end of life

• Setting: Patients attending a regional cancer associated thrombosis clinic
• Follow up over two years
• Notes review of patients at end of life
• Demographics, when anticoagulation stopped, bleeding/thrombotic complications,
• Place of death

Cancer diagnoses: n=450
Patient spread at initial review

- 44% metastatic
- 60% during chemotherapy (majority palliative)
- 59% known to specialist palliative care services

Place of death

- Home: 46%
- Hospice: 27%
- Acute Hospital: 25%
- Community Hospital: 2%
When anticoagulation stopped

- Over 1 month: 40
- 1-4 weeks: 29
- 7 days: 23
- Until death: 108
When anticoagulation stopped

- Over 1 month: 40
- 1 - 4 weeks: 29
- 7 days: 23
- Until death: 108

7%
Primary Thromboprophylaxis
Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN)

• Setting: Patients admitted to UK hospice/SPCU
• Compression ultrasonography on admission and weekly
• Screened for symptoms attributable to VTE

• Primary outcome
  • Prevalence of radiological apparent DVT

• Secondary outcomes
  • Attributable symptoms
  • Incidence of VTE and symptoms
  • Associated variables
  • Survival

White C, Noble S et al Lancet Haematology 2019
Thromboprophylaxis: Hospice Inpatient DVT Detection Study (HIDDEN

1390 screened

841 (60.5%) ineligible
- Likely to die within 5 days 397
- Physical limitations to perform ultrasonography 85
- Lacking capacity to consent/ no proxy 48
- Consultee or patient too distressed 22
- Insufficient English/ Welsh 8
- Outside of consent timeframe 245
- Non-cancer 44

Declined participation 206
Recruited 343
Demographics

• Average AKPS = 49
• Mean survival = 44 days

White C, Noble S et al *Lancet Haematology* 2019
Results: 273 evaluable scans

• 92/273 (34%, CI 28% to 40%) showed DVT.
• Excluding early scans, 64/232 (28%, 22% to 34%)

• Associated with
  • Previous thromboembolism,
  • bedbound ≤12 weeks for any reason (p=0.003)

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White C, Noble S et al Lancet Haematology 2019
No relationship with

- Serum albumin ($p = 0.430$),
- Survival ($p = 0.473$)
Tranexamic acid
Endothelial cells

**tPA**

**Plasminogen**

- Lysine-binding site
- Fibrin split products

**Plasmin**

**Fibrin**

**tPA**

**Plasminogen**

- Tranexamic acid

**Plasmin**
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

Summary
Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20,211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Findings 10,096 patients were allocated to tranexamic acid and 10,115 to placebo, of whom 10,060 and 10,067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035). The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077).
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

<table>
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<tr>
<th>Vascular occlusive events*</th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any vascular occlusive event</td>
<td>168 (1·7%)</td>
<td>201 (2·0%)</td>
<td>0·84 (0·68-1·02)</td>
<td>0·084</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>35 (0·3%)</td>
<td>55 (0·5%)</td>
<td>0·64 (0·42-0·97)</td>
<td>0·035</td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (0·6%)</td>
<td>66 (0·7%)</td>
<td>0·86 (0·61-1·23)</td>
<td>0·42</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>72 (0·7%)</td>
<td>71 (0·7%)</td>
<td>1·01 (0·73-1·41)</td>
<td>0·93</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>40 (0·4%)</td>
<td>41 (0·4%)</td>
<td>0·98 (0·63-1·51)</td>
<td>0·91</td>
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Need for transfusion and surgery. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

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Significantly reduced [493 (4.9%) vs 574 (3.7%), relative risk 0.63, 95% CI 0.70–0.96, p=0.0077].
Take home messages

1. Clots are cool
2. The clinical trials informing practice non representative populations
3. Consider stopping anticoagulants as death approaches
4. Do not give thromboprophylaxis if
   • Poor performance status (KPS<50)
   • Short prognosis
5. Tranexamic does not increase thrombotic risk
Marie Curie
Care and support through terminal illness